
N-Myc Drives Neuroendocrine Prostate Cancer Initiated from Human Prostate Epithelial Cells.

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Public Summary:

Neuroendocrine prostate cancer (NEPC) is a highly aggressive subtype of prostate cancer that is found in up to 20% of those who succumb to advanced disease. Patients diagnosed with NEPC face a dismal prognosis as there are no standard treatments due to limited insight into the biology of NEPC. Prior work has shown that the cancer gene MYCN and its protein product N-Myc are highly expressed in NEPC. However, the role of N-Myc in initiating prostate cancer and promoting NEPC has not been established. We show that the introduction of N-Myc and a second cancer gene AKT1 is sufficient to convert normal human prostate cells to NEPC with properties of rapid growth, high invasive potential, and molecular signatures of aggressive prostate cancer. We use this defined model system to demonstrate that NEPC and the most common type of prostate cancer, prostate adenocarcinoma, can both arise from the same prostate cell. The tumors require the expression of N-Myc and disruption of N-Myc levels by genetic and drug targeting leads to increased cell death and a reduction in tumor burden. Our findings establish N-Myc as a driver of NEPC and a target for future therapies.

Scientific Abstract:

MYCN amplification and overexpression are common in neuroendocrine prostate cancer (NEPC). However, the impact of aberrant N-Myc expression in prostate tumorigenesis and the cellular origin of NEPC have not been established. We define N-Myc and activated AKT1 as oncogenic components sufficient to transform human prostate epithelial cells to prostate adenocarcinoma and NEPC with phenotypic and molecular features of aggressive, late-stage human disease. We directly show that prostate adenocarcinoma and NEPC can arise from a common epithelial clone. Further, N-Myc is required for tumor maintenance, and destabilization of N-Myc through Aurora A kinase inhibition reduces tumor burden. Our findings establish N-Myc as a driver of NEPC and a target for therapeutic intervention.

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